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Progressive Cerebellar Ataxia with Variable Episodic Symptoms – Phenotypic Diversity of R1668W CACNA1A Mutation

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Key Words
Cerebellar ataxia · Eye movement disorder · Channelopathy

Abstract
We describe a family with an R1668W mutation in the *CACNA1A* gene who presented with a broader clinical spectrum and more variable features than previously reported. The mother had a pure progressive cerebellar ataxia of late onset with downbeat nystagmus, whereas her daughter suffered from episodic ataxia, hemiplegic migraine, and progressive cerebellar ataxia with horizontal gaze-evoked and rebound nystagmus. In both patients, treatment with acetazolamide was ineffective and worsened baseline ataxia, whereas flunarizine ameliorated episodic symptoms. Our report highlights profound phenotypic variability that can be associated with *CACNA1A* mutations and adds important therapeutic considerations.

Introduction

The *CACNA1A* gene on chromosome 19p13 encodes the pore-forming subunit of the P/Q-type voltage-gated calcium channel, which is expressed particularly abundantly in the cerebellar Purkinje and granule cells [1]. *CACNA1A* mutations are associated with several dominantly inherited disorders with both episodic and progressive neurological signs and symptoms, namely familial hemiplegic migraine type 1 (FHM1, MIM#141500) [2], episodic ataxia type 2 (EA2, MIM#108500) [2], spinocerebellar ataxia type 6 (SCA6, MIM#183086) [3], generalized epilepsy [4], and congenital myasthenia [5]. FHM1 is characterized by migraine attacks with ictal hemiplegia variably associated with episodic and progressive ataxia. EA2 patients experience recurrent episodes of ataxia, vertigo, nausea and fluctuating weakness. Both FHM1 and EA2 patients may have interictal nystagmus and other moderate cerebellar signs [6, 7]. SCA6 patients typically suffer from progressive cerebellar ataxia but may also have episodic ataxia [8]. Initial reports suggested that FHM1 is caused by missense and EA2 by truncation (nonsense, frameshift, splice site) mutations in the *CACNA1A* gene, while small CAG-triplet expansions resulted in SCA6 [2, 3, 6]. Subsequent reports, however, questioned this strict genotype-phenotype correlation, since there is considerable overlap of symptoms among the three allelic conditions [7–10].

We herein report on a daughter and her mother with the *CACNA1A* missense mutation R1668W, first described in other families with hemiplegic migraine variably associated with progressive ataxia, but without epi-

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sodic symptoms [6]. Furthermore, our index patient and her mother, although harboring the same mutation, are differentially affected: The daughter suffered from episodic ataxia, hemiplegic migraine, and moderate progressive cerebellar ataxia with onset in her late 20s, whereas the mother had isolated severe progressive cerebellar ataxia with onset in her late 40s. Moreover, the two family members exhibited different patterns of cerebellar ocular motor deficiencies.

Case Reports

Case 1

Over the past 9 years, the 39-year-old woman has experienced several episodes of spontaneous acute vertigo, gait ataxia, and weakness. Attacks lasted a few minutes and occurred less than once a month. The patient described spinning and see-sawing sensations during the attacks exacerbated by head movement. There were no prodromal symptoms and no other otologic or neurologic symptoms during these episodes. Since adolescence, the patient had suffered from severe and frequent migraine headaches without aura, which decreased markedly in frequency and severity after the age of 30 years. In the past 3 years she has had two attacks, lasting 10–15 min, with sudden left-sided hemiparesis, paresthesia of the left leg, and dysarthria, without associated dizziness or headaches. She has noticed slowly progressive unsteadiness of gait for 2 years. Neurological examination revealed a moderate pancerebellar syndrome with prominent ocular motor signs (table 1). Laboratory testing showed positive serum paraneoplastic cerebellar antibodies (anti-Ri). Extensive search for neoplasia, however, did not reveal any signs of a primary tumor. Brain MRI showed mild midline cerebellar atrophy. Treatment with acetazolamide up to 750 mg/day for 3 months did not reduce the frequency of attacks, and had to be stopped because of continuous dizziness, increased gait difficulties, and generalized paresthesias. Treated with the calcium channel antagonist flunarizine 5 mg/day for 9 months, the patient has experienced no more attacks of dizziness or hemiplegic migraine, while the unsteadiness of gait at baseline remained stable.

Case 2

The 73-year-old mother reported progressive gait unsteadiness starting at age 48. Over the past 3 years she was unable to walk unaided. Increasing clumsiness of the upper limbs and slurred speech developed 5 years ago. She never experienced migraine headaches, dizziness or hemiparesis. Neurological examination revealed a severe pancerebellar syndrome with only mild ocular motor abnormalities (table 1). Tendon reflexes were brisk and slightly accentuated on the left side. Plantar responses were flexor on the right side and extensor on the left side. Routine laboratory testing was normal. Testing for paraneoplastic cerebellar antibodies was negative. Cerebral MRI showed marked atrophy of cerebellar vermis and some isolated small supratentorial T_2-hyperintensities, most probably reflecting chronic vascular lesions. Treatment with acetazolamide up to 750 mg for 3 months caused the unsteady gait to markedly worsen that the patient fell repeatedly. After cessation of acetazolamide, her clinical condition returned to baseline. Treatment with flunarizine for 9 months (5 mg/day) resulted in little change in the patient's condition.

Except for the deceased grandmother of our index patient, who suffered from gait unsteadiness and dizziness in advanced age, none of the mother's siblings nor the brother of the index patient suffers from neurological symptoms.

Table 1. Clinical findings at initial assessment and Klockgether Ataxia Score at initial assessment and follow-up

		Daughter	Mother
1	Ocular motor findings		
	Horizontal gaze-evoked nystagmus	++	–
	Horizontal rebound nystagmus	+	–
	Downbeat nystagmus	–	+
	Impaired smooth pursuit eye movements	+	+
	Hypometric saccades	+	+
	Square wave jerks	–	+
2	Dysarthria	–	+++
3	Incoordination of upper and lower limbs	+	+++
4	Ataxia of gait	+	+++
5	Klockgether Ataxia Score [14]		
	Initial assessment 03/04 (no treatment)	7/35	15/35
	LAST follow-up under therapy with flunarizine 06/05	4/35	17/35

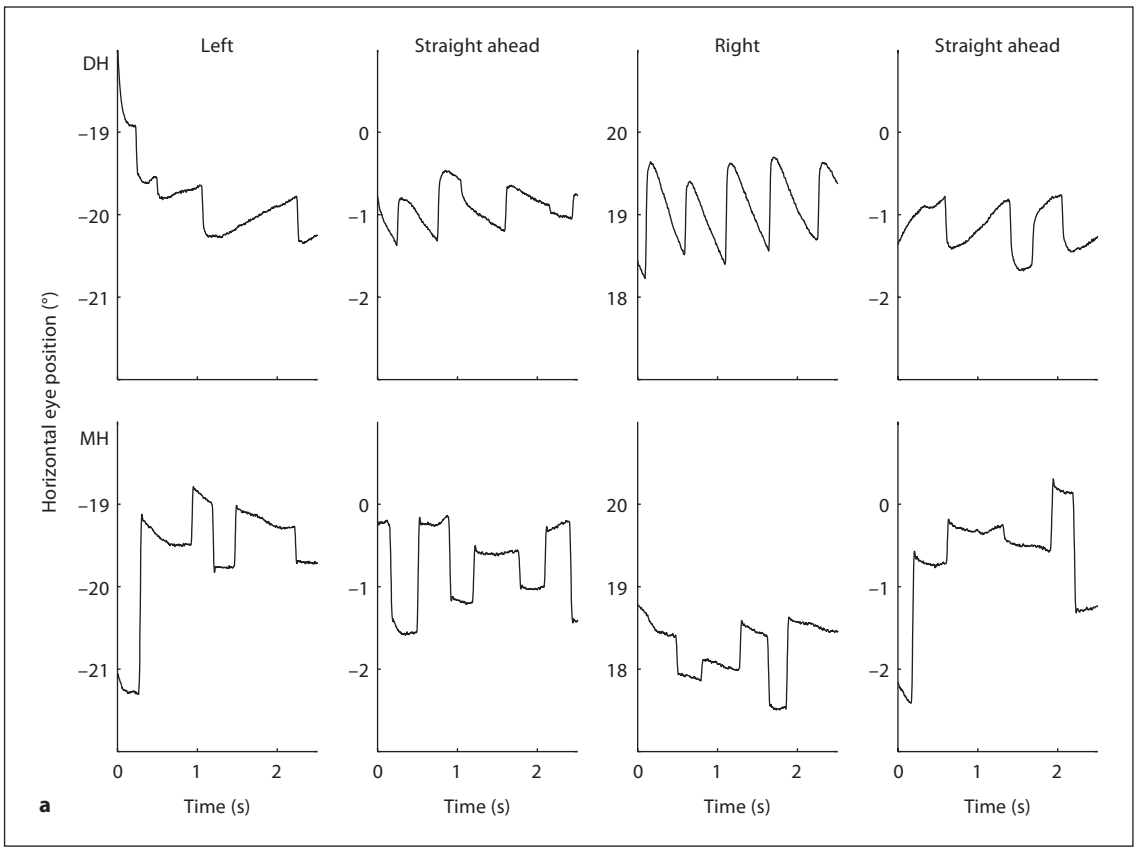
+ = Mild, ++ = moderate, +++ = severe.

Ocular Motor Findings

Horizontal and vertical eye movements (fig. 1) were recorded with magnetic search coils. Details of the search coil recordings are listed in the figure legend.

Molecular Analysis

We screened for polymorphisms in *CACNA1A* using denaturing high-performance liquid chromatography (dHPLC) followed by direct sequencing, as previously described [5]. Exon 32 showed an altered elution profile by dHPLC in the proband and her mother but not in 96 normal control subjects. Sequencing of exon 32 showed a single nucleotide change c>t at position 5250 of the coding sequence, predicting a change from arginine to tryptophan at codon 1668 in the putative S-4 voltage sensor in domain IV.



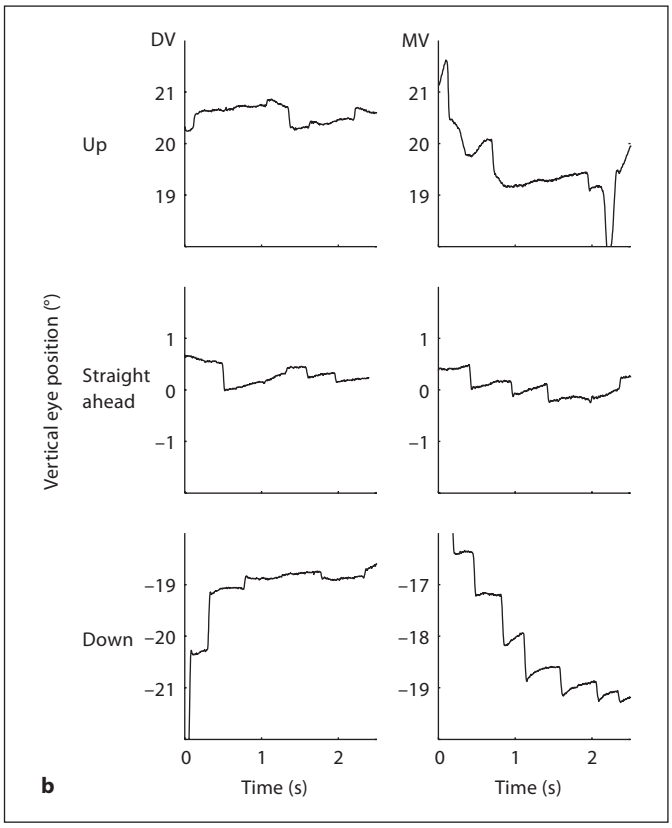


Fig. 1. a Consecutive representative sections of horizontal eye position (H) at attempted visual fixations 20° to the left (first column, 'left'), straight ahead (second column, 'straight ahead'), 20° to the right (third column, 'right'), and straight ahead again (fourth column, 'straight ahead'). Duration of sections: 2.5 s. The daughter (DH) showed prominent horizontal gaze-evoked nystagmus with centripetal ocular drift in eccentric gaze positions. When the eyes return to straight ahead, rebound nystagmus, i.e. nystagmus directed opposite of the previous gaze-evoked nystagmus, was present. The mother (MH) only exhibited minimal centripetal drift in gaze to the right and no rebound nystagmus. **b** Vertical eye position (V) at attempted visual fixations 20° up (top row, 'up'), straight ahead (middle row, 'straight ahead'), and 20° down (bottom row, 'down'). Duration of sections: 2.5 s. The mother (MV) demonstrated downbeat nystagmus in gaze straight ahead, which increased in downgaze and decreased in upgaze. Downbeat nystagmus was not present in the daughter (DV).

Discussion

We report a family with the *CACNA1A* missense mutation R1668W. While our index patient had a particular phenotype with combined features of hemiplegic migraine, episodic ataxia, and progressive ataxia, her mother suffered from pure progressive cerebellar ataxia without episodic symptoms and without migraine.

A disease-causing role of the R1668W mutation in our patients is very likely, since this mutation has been previously described in a family with pure hemiplegic migraine and another with hemiplegic migraine and permanent cerebellar signs [6], and screening for polymorphisms in *CACNA1A* was negative in 96 control subjects. Presumably, the mutation leads to altered channel kinematics since it predicts an amino acid exchange in the putative S-4 voltage sensor in domain IV of the P/Q-type voltage-gated calcium channel.

Our cases illustrate the broad clinical spectrum and variable symptomatology associated with *CACNA1A* mutations. This is in line with previous reports demonstrating phenotypic variability of *CACNA1A* mutations, hampering a simple genotype-phenotype correlation. Indeed, EA2 phenotypes are associated with nonsense and missense mutations as well as CAG-triplet repeat expansions [6, 7, 9]. On the other hand, *CACNA1A* missense mutations are also associated with severe progressive cerebellar ataxia with episodic vertigo and ataxia [10]. Additional genetic, for example the number of CAG repeats on the normal allele, and/or environmental factors must contribute to the phenotypic variability associated with distinct *CACNA1A* mutations.

This phenotypic diversity is reflected not only in the clinical but also in the ocular motor findings in the two affected family members. The index patient showed marked horizontal gaze-evoked and rebound nystagmus, whereas the mother exhibited square wave jerks and spontaneous downbeat nystagmus. We therefore speculate that, in the 2 patients, the R1668W mutation differentially alters the function of vestibulo-cerebellar structures, especially the flocculus. While gaze-evoked and rebound nystagmus indicates a failure of gaze-holding mechanisms, downbeat nystagmus suggests primarily a dysfunction of vertical gaze-velocity sensitive Purkinje cells [11].

The finding of elevated anti-Ri antibodies in the index patient may be suspicious for paraneoplastic cerebellar degeneration, yet the patient did not manifest opsoclonus, myoclonus, or dystonia, symptoms which are often associated with anti-Ri antibodies [12]. Furthermore, the temporal progression of her symptoms is far less pronounced than what is typically found in paraneoplastic cerebellar degeneration, and extensive tumor screening in the patient has remained negative. Whether the anti-Ri antibodies in our index patient play a primary pathogenic role, or whether they are a secondary phenomenon caused by an unusual epitope presentation in the context of a neurodegenerative process, remains unresolved. Also, we can only speculate whether the presence of anti-Ri antibodies, at least in part, may have contributed to the phenotypic diversity between mother and daughter.

This report also raises important therapeutic considerations. Therapeutic interventions in other families harboring the R1668W mutation have not been described [6]. In our index patient and her mother, treatment with acetazolamide was ineffective for the episodic neurological symptoms and even exacerbated baseline cerebellar symptoms. By contrast, the calcium channel antagonist flunarizine was effective in controlling episodic symptoms without worsening of progressive symptoms. Successful treatment with flunarizine was previously described in a boy suffering from periodic ataxia without any sign of progressive cerebellar disease; however, this report appeared before the genetic characterization of EA2, and whether this boy had a mutation in *CACNA1A* cannot be determined [13]. Our experience with the index patient in this report compels us to propose that flunarizine be considered in EA patients who do not respond to acetazolamide. A different effect of the drugs on specific channel kinematics seems likely.

In conclusion, we confirm that *CACNA1A* mutations are associated with considerable phenotypic variability, even within family members harboring the same mutation. Further studies will be necessary to elucidate the basis of this phenotypic variability of *CACNA1A* mutations.

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